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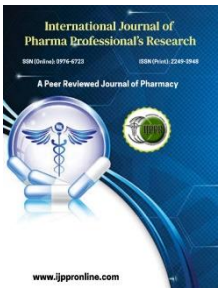

The diverse marketed formulations of advanced nano drug carrier vehicles (CVS) in different biomedical treatments: a complete descriptive review

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Keywords:
Niosomes (non-ionic vesicles), novel carriers, phytosomes, novel drug delivery systems (NDDSs), phospholipidic carriers.

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ABSTRACT: The field of pharmaceutical science and drug delivery has seen a remarkable transformation in recent years, marked by the emergence of diverse advanced approaches in the development of Novel Drug Delivery Systems (NDDs) and their associated carriers. Nanocarriers are tiny particles that can be used to deliver drugs to the body. They are typically less than 100 nanometres in diameter, which is about 1,000 times smaller than the width of a human hair. NDDs play a pivotal role in enhancing the therapeutic efficacy, safety, and patient compliance of pharmaceuticals. The research community has increasingly focused on creating novel drug delivery systems to address the limitations of conventional drug administration methods. The diversification of these approaches is notable, reflecting the interdisciplinary nature of pharmaceutical sciences. NDDs can be used to deliver drugs to specific sites in the body, control the rate of drug release, and protect drugs from degradation. Carriers play an important role in NDDs. The main highlights of the review articles in to focus on the diverse nano drug carriers including niosome, liposome, aquasome, nanoparticles (NPs) and phytosomes with their marketed available different products with their specified disease targeting.

1. Introduction

A Novel Drug Delivery System (NDDS) refers to innovative approaches and technologies designed to deliver pharmaceutical compounds in a targeted and controlled manner to enhance the therapeutic efficacy and safety of drugs. Traditional drug delivery systems often involve simple methods like oral tablets or capsules, which may result in systemic distribution of the drug and potential side effects. NDDS allows for specific targeting of drugs to the desired site of action within the body, reducing systemic exposure and minimizing side effects.

NDDS aims to overcome limitations associated with conventional drug delivery by providing more precise control over the release, targeting,

and absorption of drugs. Novel drug delivery systems (NDDSs) are a rapidly growing field of pharmaceutical research and development. NDDSs are designed to improve the efficacy, safety, and patient compliance of existing drugs, as well as to deliver new drugs that are not possible with conventional drug delivery systems.[1-2]

1.1 Classification of NDDS

NDDSs can be classified into two main categories:

1.1.1 Controlled drug delivery systems

These systems release the drug at a predetermined rate over some time. This can be achieved using a variety of mechanisms, such as diffusion, osmosis, and biodegradation.

1.1.2 Targeted drug delivery systems

These systems deliver the drug to a specific site in the body. This can be achieved by using drug carriers that are specific to certain tissues or cells, or by using external stimuli, such as magnetic fields or ultrasound, to guide the drug to its target site.[3-4]

NDDSs include various drug delivery systems containing *niosomes, liposomes, nanoparticles, aquasomes and phytosomes*.[2-5] These has been discussed in detail as follows and shown as per Figure 1.

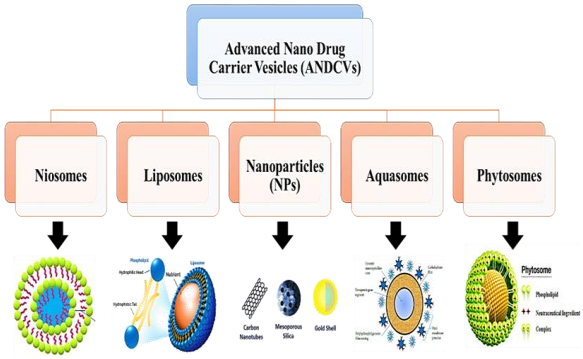

Figure 1: The various ANDCVs carrier with their basic structure forms

Niosomes are non-ionic surfactant vesicles. They are similar to liposomes, but they are made with non-ionic surfactants instead of phospholipids. This makes them more stable and less expensive to produce than liposomes.[6] Niosomes can be used to deliver a variety of drugs, including peptides, proteins, and nucleic acids.[6-7] ***Liposomes*** are tiny sacs made of phospholipids. Phospholipids are the same type of molecules that make up cell membranes. This makes liposomes biocompatible and non-toxic. Liposomes can be used to encapsulate drugs and protect them from degradation.[8] Liposomes can also be used to target drugs to specific sites in the body by attaching targeting ligands to their surface. [8-9] ***Nanoparticles (NPs)*** are tiny particles that are less than 100 nanometers in diameter. They can be made from a variety of materials, including lipids, polymers, metals, and ceramics.[10] NPs can be used to deliver drugs, vaccines, and other therapeutic agents to the body. NPs can also be used to target drugs to specific sites in the body and control the rate of drug release.[11-12] ***Aquasomes*** are nanoscale vesicles made of hydrated phospholipid bilayers. They are similar to liposomes, but they are more stable and less expensive to produce.[13] Aquasomes can be used to deliver a variety of drugs, including peptides, proteins, and nucleic acids.[13-14] ***Phytosomes*** are complexes of plant extracts and phospholipids. They are more stable and bioavailable than plant extracts alone. Phytosomes can be used to deliver a variety of plant-based compounds, including antioxidants, flavonoids, and carotenoids. [15-19]

The several compositions of the various nano drug carrier for the drug delivery mentioned in the given Table. 1 as below section

Table. 1: The list of differences between the Niosomes, liposomes, phytosomes and aquasomes [6-19]

Component	Nanoparticle (NPs)	Liposome	Niosome	Phytosome	Aquasome
Main component	Organic or inorganic	Phospholipids	Non-ionic	Phytosterols and phosp	Phospholipid

	material s		surfac tants	holipid s	s and water
Other comp onent s	Polyme rs, metals, semicon ductors, etc.	Choles terol, triglyc erides, polym ers, etc.	Chole sterol, triglyc erides, polym ers, etc.	Choles terol, triglyc erides, polym ers, etc.	Choles terol, triglyc erides, polym ers, etc.
Size	1-1000 nm	20-1000 nm	20-1000 nm	20-1000 nm	20-1000 nm

2. Niosomes (Non-Ionic Surfactant Vesicles)

2.1 Non-ionic surfactants

Non-ionic surfactants form the bilayer structure of niosomes, which encapsulates the drug and protects it from degradation. Non-ionic surfactants also play a role in the targeting of niosomes to specific cells and tissues. Examples of non-ionic surfactants used in niosomes include Span 60, Span 80, Tween 20, and Tween 80.

2.2 Cholesterol

Cholesterol is incorporated into niosomes to enhance their stability and rigidity, a crucial factor in preventing undesired fusion or collapse of the niosomes. Additionally, cholesterol plays a significant role in regulating the controlled release of drugs from niosomes.

2.3 Charge-inducing agents

These agents are added to niosomes to improve their stability and to target them to specific cells and tissues. Examples of charge-inducing agents used in niosomes include dicetyl phosphate (negative charge) and stearyl amine (positive charge). It can be applicable as negatively charged niosomes can be used to target positively charged cancer cells.

2.4 Drugs

Niosomes can be used to deliver a wide range of drugs, including small molecules, peptides, proteins, and nucleic acids.[20-22]

Niosomes, an advanced drug delivery system, represent a promising technology in the field of pharmaceuticals. These are nano-sized vesicles composed of non-ionic surfactants and cholesterol, forming a bilayer structure akin to liposomes. The unique feature of niosomes lies in their ability to encapsulate both hydrophilic and hydrophobic drugs, offering versatility in drug delivery. Their biocompatibility, stability, and low toxicity make them attractive candidates for enhancing drug efficacy and minimizing side effects. Niosomes can improve the bioavailability of drugs, protect them from degradation, and enable controlled release, leading to sustained therapeutic effects. Additionally, the surface properties of niosomes can be modified to achieve targeted drug delivery, ensuring drugs reach specific tissues or cells, thereby optimizing treatment outcomes.[23] The basic structure of niosome with their all compositional parts as per Figure 2 with their descriptive as below followings

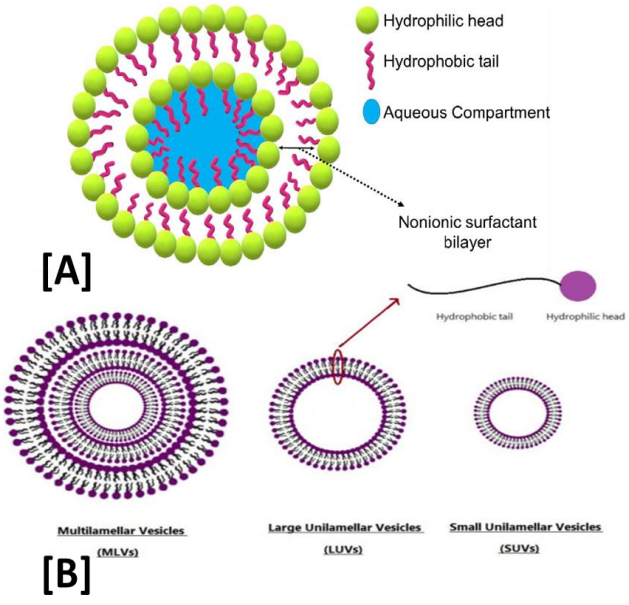

Figure 2: The basic structural representation; [A]. The simple compositional form of niosome with their all parts, [B]. The classification of niosome as per their sizes

Niosomes are non-ionic surfactant vesicles that are used as a novel drug delivery system. They are composed of a bilayer of non-ionic

sufactants, such as Span 60 and Sorbitan monostearate, and cholesterol. Niosomes are similar to liposomes, but they are more stable and less expensive to produce. Niosomes can be used to deliver a wide variety of drugs, including both hydrophilic and lipophilic drugs. They can also be used to deliver drugs to a variety of tissues and organs.[24-25] Niosomes offer a number of advantages over traditional drug delivery systems, including

- **Improved solubility and bioavailability**

Niosomes can improve the solubility and bioavailability of poorly soluble drugs. This is because the drug is encapsulated inside the niosome vesicle, which protects it from degradation and enhances its absorption into the bloodstream.

- **Targeted drug delivery**

Niosomes can be modified to target specific tissues and organs. This can be done by attaching ligands to the surface of the niosomes that bind to receptors on the target cells.

Controlled release

Niosomes can be designed to release drugs in a controlled and sustained manner. This can help to reduce the side effects of drugs and improve their therapeutic efficacy.[26]

Niosomes are being investigated for a variety of therapeutic applications, including, cancer treatment to deliver anticancer drugs to tumor cells, while minimizing the exposure of healthy cells to the drug.[27] Gene therapy to deliver gene therapy vectors to cells. This could be used to treat a variety of genetic disorders.[26-27] Ocular drug delivery for deliver drugs to the eye. This could be used to treat a variety of eye diseases, such as glaucoma and macular degeneration and transdermal drug delivery to deliver drugs through the skin.[28] This could be used to treat a variety of conditions, such as pain, inflammation, and skin infections.

The several marketed products with their disease targeting and different route of administration mentioned in the given Table. 2 as followings

Table. 2: The list of clinical Trials of niosomal products with their route of administration and disease specified [23-29]

Niosomal formulation	Phase of clinical trial	Route of administration	Disease
Niosomes containing doxorubicin	Phase II	Intravenous	Breast cancer
Niosomes containing amphotericin B	Phase II	Intravenous	Visceral leishmaniasis
Niosomes containing 5-fluorouracil	Phase II	Topical	Actinic keratosis
Niosomes containing retinol and Hyaluronic acid	Phase II	Topical	Acne/Dry Skin

Niosome are widely used for the treatment of several disease with their different products discussed above description. The some other marketed products like ***Evasone (clobetasone 17-propionate)*** is a niosomal cream that is used to treat a variety of skin conditions, such as eczema, psoriasis, and dermatitis[29] and ***Amnoniacal Silver Nitrate (0.1%)*** a different

niosomal eye drop that is used to treat bacterial conjunctivitis in newborns.[30] In addition to these marketed products, there are a number of niosomal products that are currently in clinical trials. These products are being investigated for a variety of therapeutic applications, including cancer treatment, gene therapy, and vaccine delivery.[30-33]

3. Liposomes (Phospho-lipidic Vesicles)

Liposomes are spherical vesicles composed of one or more phospholipid bilayers. They can be used to encapsulate a wide range of therapeutic agents, including small molecules, peptides, proteins, and nucleic acids. Liposomes have emerged as a versatile drug delivery system due to their unique properties, like as biocompatibility, safety, encapsulate a wide range of drugs, targeted specific cells and tissue and controlled drug release.[33-35] Liposomes are vesicular drug delivery systems that consist of phospholipid bilayers. The main components of liposomes are

3.1 Phospholipids

These are the main components of liposomes and form the bilayer structure. Examples of phospholipids used in liposomes include phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine.

3.2 Cholesterol

Cholesterol is added to liposomes to improve their stability and rigidity.

3.3 Charge-inducing agents

These agents are added to liposomes to improve their stability and to target them to specific cells and tissues like Dicetyl phosphate and stearylamine.

3.4 Drugs

Liposomes can be used to deliver a wide range of drugs, including small molecules, peptides, proteins, and nucleic acids.[36]

The basic structure of liposomes with their all compositional parts and classification of it's depending on their size as per the Figure 3 with their descriptive as below followings

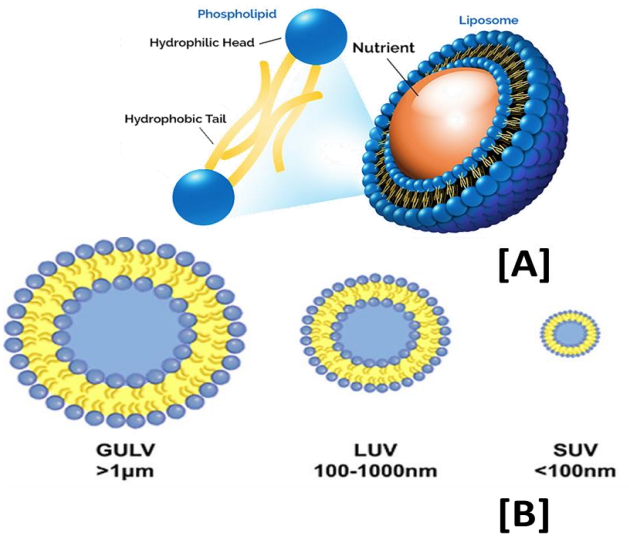

Figure 3: The description of liposome figure included [A]. The basic structure of liposome and [B]. The liposomal classification depends on their size (GULV, LUVs and SUVs)

Liposomes are used in drug delivery because they can encapsulate a wide variety of drugs, including small molecules, peptides, proteins, and nucleic acids. The drug can be loaded into the aqueous core of the liposome or into the lipid bilayer, depending on the drug's properties. Once loaded with a drug, liposomes can be injected into the bloodstream or applied to the skin. The liposomes will circulate in the bloodstream until they reach the target tissue. Once there, the liposomes can be taken up by cells or release the drug into the surrounding tissue.[36-38]

Liposomes have been used to deliver a wide range of drugs for a variety of diseases, including cancer, infectious diseases, and neurological disorder. The most notable examples of marketed liposomal drug products included in the Table. 3 as below followings

Table. 3: The marketed products of liposomes with its route of administration and application

Marketed Product	Route of administration	Application
Doxil	Intravenous infusion	Treatment of ovarian cancer, multiple myeloma, and Kaposi's sarcoma[35]
AmBisome	Intravenous infusion	Treatment of serious fungal infections, such as invasive aspergillosis and mucormycosis
DepoDur	Intramuscular injection	Long-term pain relief for patients with chronic pain
DepoCyt	Intrathecal injection	Treatment of acute myeloid leukemia and lymphomatous meningitis
Myocet	Intravenous injection	Treatment of advanced prostate cancer
Mepact	Intravenous infusion	Treatment of small cell lung cancer
Marqibo	Intravenous infusion	Treatment of acute myeloid leukemia
DaunoXome	Intravenous infusion	Treatment of acute myeloid leukemia
Visudyne	Intravitreal injection	Treatment of choroidal neovascularization due to age-related macular degeneration and pathologic myopia
Arikayce	Intravenous infusion	Treatment of nosocomial bacterial pneumonia and ventilator-associated pneumonia caused by Pseudomonas aeruginosa
Expel	Topical application	Treatment of head lice
Inflexal V	Intravenous (IV) infusion	Treat a variety of inflammatory conditions, including Crohn's disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis[36-40]

Liposomes are a versatile drug delivery system with the potential to revolutionize the way we treat diseases. They are already being used to deliver a wide range of drugs for a variety of diseases, and there are many other liposomal drug products in development.[39]

4. Nanoparticles (NPs)

Nanoparticles are having a major impact on the field of medicine. They are being used to develop new drugs, diagnostic tools, and imaging agents. Nanoparticles play a crucial role in drug delivery, offering a promising avenue for improving the efficacy and safety of various therapeutic agent.[40]

Nanoparticles are tiny particles with dimensions typically ranging from 1 to 100 nanometers. They can be made from various materials, including polymers, lipids, metals, and ceramics. The nanoparticles (NPs) challenging as biocompatibility to ensuring that nanoparticles are biocompatible and do not cause toxicity is a significant challenge.[41] Regulatory approval for nanoparticles in drug delivery can be complex due to safety concerns and a lack of standardized testing methods and scalability of nanoparticle (NPs) production methods may not be easily scalable for mass production.

Nanoparticles are also being investigated for use in a variety of other medical applications, such as

- **Tissue engineering**

Nanoparticles can be used to create scaffolds for tissue engineering and to deliver stem cells to damaged tissues.

- **Gene therapy**

Nanoparticles can be used to deliver genes to cells for therapeutic purposes.

- **Vaccine development**

Nanoparticles can be used to develop new vaccines that are more effective and less expensive than traditional vaccines.[42-45]

The basic structure of Nanoparticles (NPs) with their all-compositional parts and classification of it's depending on their size as per the Figure 4 with their descriptive as below followings

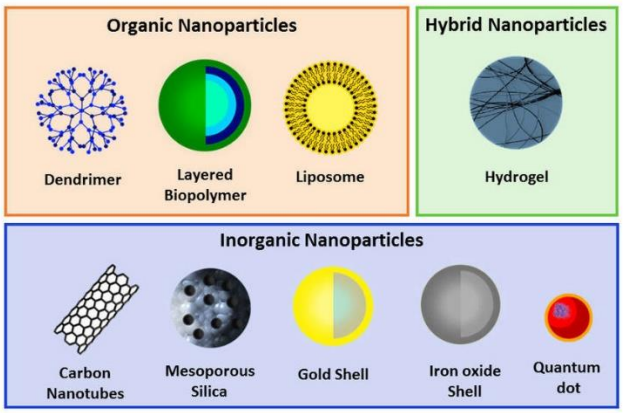

Figure 4: The different types of NPs with their categories on its several sizes

The applications of nanoparticles in medicine can be drug delivery that improve the efficacy of drugs and reduce side; as diagnostic tools in cancer and Alzheimer's disease as nanoparticles can be used to image tumors or to detect the presence of disease-specific markers in the blood.[45-49] The several marketed products of NPs with their different applications shown in the given Table. 4 as below followings

Table 4: The list of marketed products of nanoparticles (NPs) with its route of administration and application in detail

Marketed Product	**Route of administration**	**Application**
Doxil (doxorubicin liposome injection)	Intravenous	Treatment of breast cancer, AIDS-related Kaposi's sarcoma, and ovarian cancer[44]
Invega Sustenna (paliperidone palmitate	Intramuscular	Treatment of schizophrenia and

microspheres)		schizoaffective disorder
Neulasta (pegfilgrastim injection)	Subcutaneous	Treatment of chemotherapy-induced neutropenia
Onpattro (patisiran injection) and Onivyde (irinotecan liposome injection)	Intravenous	Treatment of hereditary transthyretin-mediated amyloidosis and metastatic pancreatic cancer
Sprycel (dasatinib tablets)	Oral	Treatment of chronic myeloid leukemia (MCL) and Philadelphia chromosome-positive acute lymphoblastic leukemia
Vectibix (panitumumab injection)	Intravenous	Treatment of colorectal cancer [44-48]

The utilization of nanoparticles in drug delivery holds immense potential to transform the medical field by enhancing treatment efficacy and mitigating adverse effects. Nanoparticles represent a promising novel drug delivery system that can enhance the management of diverse ailments.[50-54]

5. Aquasomes

Aquasomes is an advanced drug delivery system that is made up of a solid core surrounded by a water-soluble shell. The solid core can be made of a variety of materials, such as calcium phosphate or ceramic diamond. The water-soluble shell is made up of carbohydrates, such as dextran or chitosan. Aquasomes are unique in that they can be used to deliver a wide range of drugs, including small molecules, peptides, proteins, and nucleic acids. They can also be targeted to specific cells and tissues in the body.[55-59] Aquasomes are a type of nanovesicular DDS that consists of a solid core made of a biodegradable polymer, such as poly (lactic-co-glycolic acid) (PLGA), coated with a carbohydrate layer, such as lactose.

The core can be loaded with a variety of drugs, including small molecules, peptides, proteins, and nucleic acids.[60] The basic structure of aquasome in to nano drug delivery shown in the given Figure 5 as below description

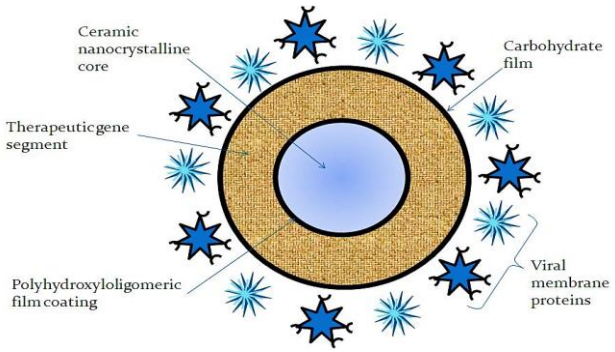

Figure 5: The basic structural composition of liposome as nano drug delivery carrier

The different types of clinical trials medication to treat different disease with their phase and applications shown as per the Table. 5 as below followings

Table. 5: The list of aquasomes that is under the clinical trials with their specified disease or applications[61-65]

Clinical Trial	Phase	Application
A Phase I/II Clinical Trial to Evaluate the Safety and Efficacy of Aquasomes Containing	I/II	Cancer [52]

Doxorubicin for the Treatment of Advanced Solid Tumors		
A Phase I/II Clinical Trial to Evaluate the Safety and Efficacy of Aquasomes Containing Vancomycin for the Treatment of Sepsis	I/II	Infectious Diseases[55]
A Phase I/II Clinical Trial to Evaluate the Safety and Efficacy of Aquasomes Containing Insulin-like Growth Factor-1 (IGF-1) for the Treatment of Alzheimer's Disease	I/II	Neurological Disorders[56]
A Phase I Clinical Trial to Evaluate the Safety and Efficacy of Aquasomes Containing a Novel Drug for the Treatment of Parkinson's Disease	I	Neurological Disorders[50]
A Phase I Clinical Trial to Evaluate the Safety and Efficacy of Aquasomes Containing a Novel Drug for the Treatment of Multiple Sclerosis	I	Neurological Disorders[59]

The phase of a clinical trial indicates how far along the drug development process is. Phase I clinical trials are the first trials in humans and are designed to assess the safety of a new drug. Phase II clinical trials are designed to assess the efficacy of a new drug and to further evaluate its safety. Phase III clinical trials are designed to compare a new drug to an existing standard of care treatment.[50-54]

Aquasomes represent a highly promising drug delivery system that holds the potential to significantly enhance the treatment of a wide range of diseases.

6. Phytosomes

Phytosomes are a type of liposome that contains a complex of a phospholipid and a phytosomal compound, such as a flavonoid or herbal extract. Aquasomes are a type of niosome that is prepared with a high proportion of water. This makes them more suitable for delivering hydrophilic drugs.

Phytosomes are a type of drug delivery system that combines a phytochemical (a plant-based compound) with a phospholipid (a type of fat). The phospholipid surrounds the phytochemical, forming a micelle-like structure. This structure protects the phytochemical from degradation and helps it to be absorbed more easily by the body. Phospholipids are the main building blocks of cell membranes and are biocompatible and biodegradable.[66-69] When phytosomes are administered to the body, they are easily absorbed into the bloodstream and delivered to the target tissues.

6.1. Composition: Phytosomes consist of a complex formed by binding or encapsulating bioactive phytoconstituents, such as plant extracts or herbal compounds, with phospholipids. Phospholipids are natural lipids that have a hydrophilic (water-attracting) head

and a hydrophobic (water-repelling) tail. This unique structural arrangement allows them to form liposomal complexes with phytoconstituents, creating phytosomes.[70-72] The basic structure of phytosomes as nano drug delivery carrier or vesicles and they are similar to the liposome then the difference between the liposome and phytosomes is shown in Figure 6 as below followings

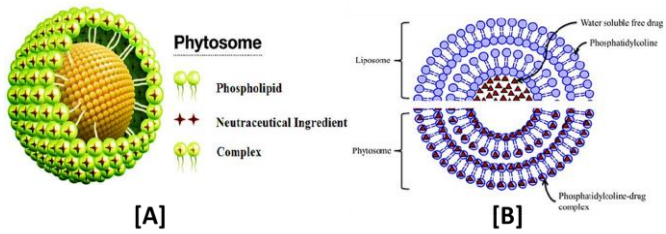

Figure. 6: The structural representation including; [A]. The basic structure of phytosomes with loaded nutraceutical ingredients, [B]. The structural representation of liposome and phytosomes differentiation

These innovative nano drug carriers have gained prominence in the field of pharmaceuticals and nutraceuticals due to their ability to address the challenges associated with the poor solubility and absorption of certain phytoconstituents.[73-75] The several marketed products of the phytosomes with different route of administration shown as per the Table. 6 as below description

Table. 6: The list of marketed products of liposomes with its route of administration and applications [70-76]

Marketed Product	Route of administration	Application
Silymarin Phytosome®	Oral capsule	Treatment of liver disease, such as hepatitis and cirrhosis [59]
Leucoselect® Phytosome®	Oral capsule	Treatment of chronic venous insufficiency and lymphedema [60-61]
Greenselect® Phytosome®	Oral capsule	Weight management and antioxidant protection[63]
Curcumin Phytosome®	Oral capsule	Treatment of inflammation, arthritis, and cancer[65]
Pycnogenol®	Oral capsule	Treatment of chronic venous insufficiency, hypertension, and erectile dysfunction[69]
Hawthorn Phyto-some®	Oral capsule	Treatment of heart failure and arrhythmia[70]

Phytosomes are already being used to treat a variety of diseases, and there are many other phytosomal products in development. Phytosomes have the potential to revolutionize the way we use phytochemicals to improve human health. Phytosomes are a promising and versatile class of nano drug carriers that play a vital role in improving the bioavailability and effectiveness of bioactive compounds, particularly those derived from plants.[77-78] Their unique composition and benefits make them a valuable tool in the fields of pharmaceuticals, herbal medicine, nutraceuticals, and cosmeceuticals, offering a potential solution to the challenges of poorly water-soluble compounds in drug delivery.[79-82]

7. Future Directions

The future of ANDCVs is very promising. Researchers are constantly developing new and

improved ANDCVs with new and innovative functionalities. For example, some researchers are developing ANDCVs that can be triggered to release their drug cargo in response to specific stimuli, such as changes in pH or temperature. Other researchers are developing ANDCVs that can be used to deliver multiple drugs simultaneously.

ANDCVs are also being investigated for new and emerging applications, such as personalized medicine and theranostics. Personalized medicine is an approach to healthcare that tailors treatments to the individual patient, based on their unique genetic and molecular profile. Theranostics is an approach that combines diagnostics and therapeutics into a single platform. ANDCVs have the potential to play a major role in personalized medicine and theranostics.

8. Conclusion

Advanced nano drug carrier vehicles represent a paradigm shift in the field of biomedical treatments. Marketed formulations of diverse nanocarriers are being harnessed to overcome the limitations of traditional drug delivery systems. These advanced nano drug carriers hold immense promise in targeted drug delivery, enhanced bioavailability, and reduced side effects. Their versatility and adaptability to various therapeutic agents make them invaluable tools in modern medicine. In conclusion, the remarkable potential of advanced nano drug carriers is transforming the landscape of biomedical treatments, opening new avenues for improving patient outcomes and enhancing the quality of healthcare. The completer description of all nano drug carrier discussed in the above mentioned description with their complete marketed drug products.

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10. Authors Contribution: This project was undertaken through a collaborative endeavor involving all four authors, encompassing the conceptualization and design of the study, data collection, compilation, analysis, and interpretation, as well as the composition, critical evaluation, and ultimate endorsement of the final manuscript.

11. Conflict of Interests: All authors have none to declare.

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